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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,739	03/14/2002	Masayuki Amagai	201487/1070	5390

7590 09/23/2004

Michael L Goldman
Nixon Peabody
Clinton Square
PO Box 31051
Rochester, NY 14603

EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,739	AMAGAI ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8, 11-16, 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-8,11-16 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 6, 2004 has been entered.

The amendment, response, and the second Declaration of Masayuki Amagai under 37 CFR § 1.132 have been entered. Claims 2, 3, and 11 have been amended. Claims 9, 10, 17, 18, 24, and 25 have been canceled. Claims 2-8, 11-16, 19-23 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims, and new grounds of rejection will not be reiterated. The arguments in 7/6/04 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-4, 6, 11, 12, 14, 19, 23 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

These claims are directed to a mouse recipient transplanted with immune cells from a mouse donor that lacks a gene encoding an auto-antigen protein and immunocompetent; and a method for producing the recipient mouse. Given the broadest reasonable interpretation in light of the specification, the claims encompass making various autoimmune disease models for any auto-antigen of interest, and production of such autoimmune disease models would require the use of numerous gene knockout mice in which a gene encoding an auto-antigen is functionally disrupted.

Thus, one of the critical steps for producing the claimed recipient mouse is the availability of a mouse donor that lacks a gene encoding an auto-antigen protein and immunocompetent, i.e. whether the starting materials for practice the invention is readily available to the public. To this end, the specification teaches using a Dsg3-/- mouse (knockout for Dsg3 gene) for establishing a pemphigus vulgaris model in immunodeficient RAG2-/- mice, and contemplating that the method of the present invention can be widely applicable to the preparation of model animals for other autoimmune disease in which associated autoimmune targets have been identified (Specification, pages 5-6). However, the specification fails to provide an adequate written description for with regard to the starting materials for making the genus of antoimmune disease models, i.e. gene knockout mice for other known auto-antigens in terms of distinguishing characteristics of the knockout mice. Accordingly, the specification fails to provide an adequate written description for what is now claimed.

In the newly submitted declaration, the applicant provided a list of 11 transgenic mice that are knockout for certain type of auto-antigens. However, it is noted only three lines of mice on the list are generated prior to the effective filing date. The other eight knockout lines are produced after the effective filing date, and thus fail to provide an adequate written description to support the instant disclosure because the standard for evaluating the adequacy of a disclosure under 35 USC 1st paragraph is "at the time of the invention". The court has ruled (*In re Glass*, 181 USPQ 31, (CCPA 1974)), IF A DISCLOSURE IS INSUFFICIENT AS OF THE TIME IT IS FILED, IT CANNOT BE MADE SUFFICIENT, WHILE THE APPLICATION IS STILL PENDING BY LATER PUBLICATIONS WHICH ADD TO THE KNOWLEDGE OF THE ART SO THAT THE DISCLOSURE, SUPPLEMENTED BY SUCH PUBLICATIONS, WOULD SUFFICE TO ENABLE THE

PRACTICE OF THE INVENTION. INSTEAD, SUFFICIENCY MUST BE JUDGED AS OF THE FILING DATE; SECTION 132 PROHIBITS ADDING NEW MATTER TO DISCLOSURE AFTER FILING" (emphasis added). The fact that the specific mice are not disclosed in the specification indicates that the specification does not support the claims as filed, but instead reflects further critical information is essential for the artisan to practice the invention. Since the starting materials for making the broadly claimed class of autoimmune diseases are absent from the specification, the disclosure of the specification fails to provide an adequate written description to support the full scope of the invention, and the suffice of the disclosure could not relied on the post-filing date publications.

With respect to the three mouse lines that were made before the effective filing date, it is noted that the cited references did not describe whether the knockout mice develops immune cells as required by the instant claims. Assuming they do develop immune cells, the publications fail to disclose whether such immune cells are capable of inducing an autoimmune disease upon adoptive transfer, which is another critical characteristic required for the production of the claimed recipient mice. Moreover, it is noted that out of the three mouse lines, two of them belong to cytochrome P450 family of enzymes which may be associated with the hepatitis in autoimmune polygandular syndrome (APS). However, such association was established on the basis of detectable autoantibodies in isolated human subjects (only one in the cited publication), there is no evidence of record nor the specification teaches that the immune cells from the knockout mice would transfer an autoimmune hepatitis (see more discussions in the

following section). Thus, these publications fail to provide a sufficient support for the broad claims.

In analyzing whether the written description requirement is met for the claimed subject matter i.e. a genus of models for autoimmue diseases, a representative number of species is need by the distinguished disease phenotype and genotype of the mice, and other relevant identifying characteristics, such as the ability to induce an autoimmune disease. The claimed genus encompasses any autoimmune disease model of the mouse. However, the only disclosed species in the specification is the DSG3-/- mouse. Considering the numbers and variety of autoimmune diseases, thus, the number of required knockout mice, the one exemplary embodiment is not the representative species of the genus.

An adequate written description for a knockout mouse requires more than a mere statement that it is part of the invention; what is required is a description of the genotype and phenotype itself. With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific genotype and phenotype (function of the immune cells) of the mouse, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). This is particularly true for the claimed knockout mice, the most sophisticated form of a combination of chemical compounds.

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436). Here, the knockout mice are the critical element, wherein the variation of the genus is attributed to at least the following factors: the genes being disrupted, the efficiency of cloning a knockout mouse, the state of immune cells of the knockout mouse, and the importance of the knockout antigen in the initiation and sustaining mechanisms of an autoimmune disease. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or using it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific knockout animals and their immune cells, which provide the means for practicing the invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION *OF THE INVENTION*. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED*." (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of or representative species of knockout mice that could be used as starting materials in the claimed method. Therefore, only the described DSG3-/- meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 2-4, 6, 11, 12, 14, 19, 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a mouse model showing a phenotype of pemphigus vulgaris by transplanting immune cells of the Dsg3-/- mouse into an immunodeficient recipient, does not reasonably provide enablement for making *any* autoimmune disease model by transplanting immune cells of a donor lacking a gene encoding *any* auto-antigen into an immune competent/deficient recipient. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

To the extent that the claimed methods are not adequately described in the instant disclosure, claims 2-4, 6, 11, 12, 14, 19, 23 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described, which is not conventional in the art.

These claims are drawn to using a knockout mouse for producing an autoimmune disease model in another mouse, however, as indicated *supra* in the written description section, the specification fails to provide an adequate description for

a critical element required for practice the invention, i.e. the broad class of knockout mice used in the method. Since the disclosure fails to describe the common attributes or characteristics of sufficient variety of species, DSG3-/- alone is insufficient to describe the genus. This is because the starting materials are not readily available to the public, and the skilled artisan cannot envision the functional characteristics of immune cells obtained from these mice, thus would not know how to use the invention without first carrying out undue experimentation to identify the most effective antigens, to clone a line of knockout mouse, to characterize the immune cells from the knockout mice, and to find out for themselves which of the immune cells could trigger an autoimmune disease. According, it would have required undue experimentation for those skilled intending to practice the invention.

With respect to the few knockout mouse lines available at the time of instant effective filing date. It is the Examiner's opinion even if the knockout mice are available in the art, it is unpredictable whether immune cells obtained from these mice would cause the correspondent autoimmune disease as desired because of the complicated nature in initiation and sustaining of an autoimmune disease, another critical element that determines the enablement or lack of for the claimed invention, and because the immune cells of these mice have not been characterized. This opinion is supported by the cited art of record such as *Janeway Jr.* and *Bach et al*, and the teaching of *Schloot et al* (J Autoimmun 1996;9:357-63), who teach that multiple antigens are associated with the pathogenesis of diabetes, such as insulin and GAD65. However adoptive transferring peripheral T cell clones specific for GAD65 failed to transfer or accelerate

diabetes into NODscid mice, whereas the T cell clone specific for insulin (PD12-4.1) did (e.g. Table 3). Apparently, the diabetogenicity of the donor immune cells varies depending on the type of auto-antigen, the functional characteristics of the immune cells, and likely other factors. Thus, it is highly unpredictable and the specification fails to teach whether the immune cells of the cited GAD_{65} -/- mouse disclosed by *Kaufman et al* (see Applicant's exhibit) could transfer diabetes upon transplantation, thus, the cited publication fails to provide sufficient support for instant claimed invention.

In the case of the autoimmune hepatitis associated with cytochrome P450 proteins, it is one of many syndromes of the APS1, an autosomal recessive disorder characterized by a variable combination of disease components (*Clemente et al*, J Clin Endocrin & Metabol 1997;82:1353-61, see Applicant's exhibit). In the publication, *Clemente et al* reported that the chronic hepatitis was observed in one of the five patients, co-existed with M. candidiasis, Addison's disease, and pernicious anemia (table 1), thus, the hepatitis occurred within the context of the combination of disease components of the APS1 as a whole. Under the circumstance, even though they have shown the autoantibody to P450 1A2 was detectable in this patient, it is not evidence that transplanting immune cells from the P450 1A2 knockout mice would induce APS1 or associated hepatitis.

In the response and declaration, applicants attempted again to extrapolate the instant disclosure for making pemphigus to the production of general autoimmune diseases (point 6). Applicant cited numerous general art insisting that the ability to create knockout animals has been known and practiced for many years, a skilled in the

art would have a high expectation of producing a viable knockout animal using the techniques known in the art (point 7-10, 13). The response also asserts that multiple antigen-knockout animals could be made if necessary.

In response, the success in the illustrated embodiment of instant specification does not support the full scope of the claims because the court has ruled that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Goodman, 29 USPQ2d 2010 (CA FC 1993); In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT." In the instant case, the genes and knockout animals involved in producing the claimed recipient mouse are the most complex forms of chemical compounds and compositions, making and using such is highly unpredictable as evidenced by the cited art of record in the previous Office

actions, and in the paragraph that follows. IN CHEMICAL CASE WHERE APPLICANT DISCLOSES THAT ONE SPECIES OF A CLASS OF CHEMICALS WILL ACCOMPLISH CERTAIN PURPOSE WITHOUT NAMING ANY OTHERS OF CLASS TO WHICH IT BELONGS OR WITHOUT SO DESCRIBING THE SPECIES AND ITS MODE OF OPERATION AS TO CALL ATTENTION TO FACT THAT OTHER MEMBERS OF CLASS ARE ITS EQUIVALENTS AND WILL PERFORM SAME FUNCTIONS, HE IS NOT ENTITILED TO BROADER SCOPE OF DISCLOSED INVENTION BY CLAIMING WHOLE GROUP EVEN THOUGH THOSE SKILLED IN ART MAY KNOW THAT IN SOME RESPECTS AT LEAST DIFFERENT MEMBERS OF GROUP ARE EQUIVALENTS; CERTAIN MEMBERS OF WELL-DEFINED GROUP OF CHEMICALS MAY BE EQUIVALENTS FOR ONE PURPOSE AND NOT EQUIVALENT FOR ANOTHER. (In re Soll, 97 F.2d623, 38 USPQ 189 (CCPA 1938).

With respect to the general references cited in the point 8 of the declaration, it is noted again that most of the references reflect the state of the art after the instant effective filing date. Further, even though the technology of knockout has advanced significantly compared to 30 years ago, the efficiency of cloning such animals is still low, whether it is producing transgeneic or knockout mice. *Yanagimachi* (Mol Cell Endocrinol 2002;187:241-8) teaches cloning efficiency, at a post-filing date, that "CLONING EFFICIENCY-AS DETERMINED BY THE PROPORTION OF LIVE OFFSPRING DEVELOPED FROM ALL OOCYTES THAT RECEIVED DONOR CELL NUCLEI-IS LOW REGARDLESS OF THE CELL TYPE (INCLUDING, EMBRYONIC STEM CELLS) AND ANIMAL SPECIES USED. IN ALL ANIMALS EXCEPT OF JAPANESE BLACK BEEF CATTLE, THE VAST MAJORITY OF CLONED EMBRYOS PERISH BEFORE REACHING FULL TERM" (Abstract), and "THUS FAR, CLONED OFFSPRING THAT SURVIVED BIRTH AND REACHED ADULTHOOD WERE THE EXCEPTION RATHER THAN THE RULE (page 243, left column, emphasis added). *Denning* (Nat Biotech 2001;19:559-562) teaches the difficulties of somatic cell cloning, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY

COULD BE PREPARED FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560). *Humpherys et al* (Science 2001;293:95-97) discuss epigenetic instability in ES cells and cloned mice, and teach, "ONLY A FEW PERCENT OF NUCLEAR TRANSFER EMBRYOS DEVELOP TO TERM. EVEN THOSE CLONES THAT SURVIVE TO TERM FREQUENTLY DIE OF RESPIRATOR AND CIRCULATORY PROBLEMS AND SHOW INCREASED PLACENTAL AND BIRTH WEIGHTS, OFTEN REFERRED TO AS 'LARGE OFFSPRING SYNDROME' " (1st paragraph, page 95), "THE EPIGENETIC STATE OF THE ES CELL GENOME WAS FOUND TO BE EXTREMELY UNSTABLE", "THESE DATA IMPLY THAT EVEN APPARENTLY NORMAL CLONED ANIMALS MAY HAVE SUBTLE ABNORMALITIES IN GENE EXPRESSION" (abstract). For these reasons, the unpredictability could be seen in both transgenic and knockout animals. *Pearson* (Nature 2002;415:8-9) teaches that in many cases, a mutant gene knockout mouse does not show any obvious characteristics or phenotype. In others, the phenotype disappears when the disabled gene is crossed into a different strain of mouse, and comments, "INDEED, CLEAR AND CONSISTENT PHENOTYPES NOW SEEM TO BE THE EXCEPTION RATHER THAN THE RULE. THESE VARIABLE RESULTS OFTEN REFLECT THE FACT THAT GENES ACTING IN PARALLEL PATHWAYS CAN COMPENSATE FOR THE ONE THAT IS MISSING" (left column, page 8). Thus, even for what is said to be "routine" procedures, it requires undue experimentation for making the donor mice and characterizing their immune cells, it is particularly difficult when multiple antigen-knockout is required, and it would require undue experimentation before the skilled could practice the claimed invention.

Claims also require transferring immune cells between mice with the same genetic background. As an initial matter, it is unclear what is considered as "the same

genetic background". If such encompasses transplantation between different individuals of the same species (allogenic transplantation), it is noted that allogenic transplantation often requires the use of immune suppressants. It is unpredictable and the specification fails to teach whether it is possible to develop an autoimmune disease model when an immune suppressant is used. Further, induction of most experimental autoimmune diseases requires the use of a genetically susceptible species of recipient animal (e.g. as indicted by *Braley-Mullen et al,* J Immunol 1994;152:307-14), and thus practicing the instantly claimed invention requires the knockout mice be made in the corresponding susceptible strains of mice, this is apparently not available at the time of the instant filing date, and the claims encompass any type of mice as recipient. In view of such, the claims do not appear to be enabled in the absence of clarification of the contradictory evidence found in the prior art.

In points 8-10, and 13 of the declaration, the applicant relies heavily on the knowledge of the skilled in the art stressing that the knockout technologies are routine, particularly the post-filing publications such as Kimball et al (2004). To this end, it is noted the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material** or of any of the conditions under which a process can be carried out, **undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.** It is the specification, not the knowledge of one skilled in the art, that must

> supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Although applicants now provide a list of publications disclosing knockout mice as potential candidate for use in the instantly claimed invention, most of them are not available until after the instant filing date, and none of them describes the immune cells of the mouse. Again, in *In re Glass*, the appellant attempted to use the disclosures of four patents issued after his filing date, and the court ruled, "IF INFORMATION TO BE FOUND ONLY IN SUBSEQUENT PUBLICATIONS IS NEEDED FOR SUCH ENABLEMENT, IT CANNOT BE SAID THAT THE DISCOSURE IN THE APPLICATION EVIDENCES A COMPLETED INVENTION... IT IS AN APPLICANT'S OBLIGATION TO SUPPLY ENABLING DISCLOSURE WITHOUT RELIANCE ON WHAT OTHERS MAY PUBLISH AFTER HE HAS FILED AN APPLICATION ON WHAT IS SUPPOSED TO BE A COMPLETED INVENTION", "IF HE CANNOT SUPPLY ENABLING INFORMATION, HE IS NOT YET IN A POSITION TO FILE.

Point 11 of the declaration discusses the technique of "adoptive transfer", which is not an issue under this rejection concerning the technique itself. The issue is the capability of immune cells in transferring disease upon transplantation such as taught by *Schloot et al* as discussed in detail above.

Point 12 of the declaration asserts that the recipient mouse need not exhibit a phenotype corresponding to a particular autoimmune disease. The argument is not persuasive because it is inconsistent with the teaching of the specification. The specification asserts the utility of the claimed mice is establishing autoimmune disease models. Thus, unless at least some of the symptoms of an autoimmune disease could be shown, the intended utility has not been enabled. The specification fails to teach the

utility of the mice without a disease phenotype, and a rejection under 35 USC § 101 may be warranted if such mice are claimed.

The court also states, "LAW REQUIRES THAT THE DISCLOSURE IN APPLICATION SHALL INFORM THOSE SKILLED IN THE ART HOW TO USE APPLICANT'S ALLEGED DISCOVERY, NOT HOW TO FIND OUT HOW TO USE IT FOR THEMSELVES" *In re Gardner* 166 USPQ 138 (CCPA) 1970. Since the instant disclosure supplemented with the prior art still require the skilled in the art to find out for themselves how to practice the claimed invention, the disclosure fails to meet the standard set forth under 35 USC § 112, 1st paragraph.

Accordingly, in view of the lack of knockout mice suitable for use in the claimed methods, the inefficiency of cloning a viable knockout mouse, coupled with the functional requirement of the immune cells from the knockout mice, and the complex nature in initiation and sustaining of an experimental autoimmune disease, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to making and using the immune cells from a knockout mouse, and the breadth of the claims directed to any autoimmune diseases, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

For reasons of record and set forth above, the rejection stands.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-8, 11-16, 19-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation, "has the same genetic background". It is unclear what the recited genetic background encompasses and excludes, and what is considered as "the same" genetic backgrounds, and thus, the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-4, 6, 19, and 21 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Schloot et al* (J Autoimmun 1996;9:357-63).

Schloot et al teach adoptive transferring (transplanting) immune cells (insulin-specific T cell clone PD12-4.1 derived from splenocytes of the donor mice) of the donor mice to recipient NOD/SCID mice (immunodeficient recipient), and upon transplantation, the recipient mice developed severe insulitis (e.g. paragraph bridging left and right columns, page 360). Thus, *Schloot et al* anticipate or in the alternative as obvious over the instantly claimed invention.

It is noted the prior art mice differ from the claimed mice only by their method of manufacture, i.e. the type of immune cells used for transplantation. However, the claimed recipient mice made by the claimed method would not distinguish them over the diabetic NOD/SCID mice made by the method taught by the prior art. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), which teaches that a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. This is because there is no evidence of record and the specification fails to teach that immune cells obtained from a knockout mouse would be structurally or functionally different from the immune cells produced by the prior art mouse. Accordingly, in the absence of evidence to the contrary, the mice taught by the prior art appear to meet instant claim limitation.

Claims 2, 3, 6, and 21 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Braley-Mullen et al* (J Immunol 1994;152:307-14).

Braley-Mullen et al teach adoptive transferring (transplanting) immune cells derived from splenocytes of donor mice immunized with MTg to recipient genetically susceptible mice, and upon transplantation, the recipient mice developed experimental autoimmune thyroiditis. Thus, *Braley-Mullen et al* anticipate or in the alternative as obvious over the instantly claimed invention.

It is noted the prior art mice differ from the claimed mice only by their method of manufacture, i.e. the type of immune cells used for transplantation. However, the claimed recipient mice made by the claimed method would not distinguish them over the mice taught by the prior art. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), which teaches that a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. This is because there is no evidence of record and the specification fails to teach that immune cells obtained from a knockout mouse would be structurally or functionally different from the immune cells produced by the prior art method, i.e. active immunized CBA/J mice. Accordingly, in the absence of evidence to the contrary, the mice taught by the prior art appear to meet instant claim limitation.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730.

The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1632

QL
September 20, 2004